natriuretic peptide, and accelerates the production of cGMP, was found to produce a decrease in cardiac weight and thus treat cardiac hypertrophy.

Applicants experimentally proved that the active component of the present invention, such as ANP, not only inhibits cardiac hypertrophy, but also decreases the cardiac weight even after the establishment of the cardiac hypertrophy. In addition, this medical effect is exhibited at a dose level which does not produce a change in blood pressure or urine volume. This shows that the present invention directly acts on the heart to prevent or inhibit cardiac hypertrophy, and does not act through natriuretic action or hypotensive action provided by the active component, such as ANP.

In their experiments, Applicants used high blood pressure model animals and volume load model animals. These experiments also confirmed that even after cardiac hypertrophy was established, administering the active components of the invention decreased the hypertrophy. *See, for example,* Example 2, pages 15-18.

Claims 6-14 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. According to the Official Action, it is not clear which particular receptor out of the plurality of natriuretic receptors is meant. This rejection is now moot in view of the instant amendment.

Claim 6 has been amended to recite that the administered substance acts on a "guanylyl cyclase a natriuretic receptor." The particular natriuretic receptor on which the substance acts is thus clear. Withdrawal of the rejection is thus respectfully requested and believed to be in order.

Claims 6-10 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Blaine et al (US Patent No. 4,652,549), as evidenced by Espiner (which is admittedly not prior art). According to the Official Action, Blaine teaches treatment of cardiac hypertrophy using atrial natriuretic peptide (ANF) and fragments thereof. Espiner is cited as teaching that ANF and analogs thereof stimulate guanylate cyclase A and production of cGMP. The Examiner alleges that since it was known that ANF and analogues thereof stimulate guanylate cyclase A and production of cGMP, the effects of ANF as claimed are inherently present. This rejection is respectfully traversed.

The experiments in Blaine et al use both hypertrophy model rats and normal rats. After administering ANP for one week, the water content in the heart (grams H_2O/100 grams tissue) was measured. In the experiment, water content was decreased upon administration of ANP. However, the decrease in water content of the heart, as disclosed in Blaine, is completely different from the repression of the hypertrophy, as discovered by Applicants. For example, *Physiology of the Heart*, A.M. Katz (ed.), pp. 397-418 (1977) (Raven Press) and *Pathophysiology of Heart Diseases,* L.S. Lilly (ed.), pp 204-205 (1998) (copies enclosed), both show that an increase in water content in the heart is *not* a cause of cardiac hypertrophy.

The disclosure in the Blaine et al reference of the ability to decrease the water content of the heart is no more than other information available in the art. *See,* for example, T. Imamura et al, *Life Sciences*, 42:403 (1988) (copy enclosed), which describes pulmonary edema inhibitory action. However, Blaine et al in no way discloses or even suggests that a substance that acts on the guanylyl cyclase A natriuretic receptor and is able to accelerate

production of cyclic guanosine monophosphate, will be effective for reducing heart weight which is not based on diuretic and hypotensive effects.

Withdrawal of the rejection of the claims over Blaine et al is thus respectfully requested. Such action is believed to be in order.

Claims 6-10 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Neustadt et al (US Patent No. 5,356,925). According to the Official Action, Neustadt et al teaches treatment of cardiovascular disorders (e.g., hypertension, congestive heart failure, renal insufficiency) using a combination of natriuretic peptide(s) and ACE inhibitor. The Official Action asserts that it was well known that ANF and analogs thereof stimulate guanylate cyclase A and production of cGMP. The treatment of cardiac hypertrophy using atrial natriuretic peptide (ANF) analogues which bind to natriuretic receptor is thus asserted to be inherently present. This rejection is respectfully traversed.

Neustadt et al discloses the use of a mixture of NEP inhibitor and ANP. The reference discloses that ANP alone is used for diuretic action and blood vessel expansion activity. These uses of ANP were known in the art prior to the Neustadt et al patent. *See, for example*, Y. Saity et al, *Circulation*, 76:115-128 (1986). Neustadt et al was thus directed to particular N-(mercaptoalkyl)ureas and carbamates and their use alone or in combination with an ANF. Neustadt et al in no way discloses or even suggests that administration of a substance which acts on guanylyl cyclase A and accelerates the production of cGMP can produce a decrease in cardiac weight and thus treat cardiac hypertrophy, as claimed by Applicants.

Since Neusstadt et al fails to disclose or even suggest Applicants' claimed invention, this reference fails to anticipate Applicants' claimed invention. Withdrawal of this rejection is thus respectfully requested and believed to be in order.

Claims 6-9 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Berman et al (JP 63303998) as evidenced by Espiner. The Official Action asserts that Berman et al teaches treatment of cardiac hypertrophy using atrial natriuretic peptide (ANF) analogues which bind to natriuretic receptor. According to the Official Action, it is "well known that ANF, as well as its analogs stimulate guanylate cyclase A and production of cGMP." The effects of ANF analogues as claimed are thus concluded to be inherently present. This rejection is respectfully traversed.

Berman et al relates to a peptide analogue, wherein the S-S bond is replaced with a carbon atom. The biological activity of the analogue, however, is not substantially described. The reference discloses that cardiac hypertrophy caused by promotion of secretion of renin-aldosterone can be treated by inhibiting activity of ANP on the secretion of renin-aldosterone. There is nothing in the reference, however, to show that the peptide analogues can be used to effectively treat cardiac hypertrophy.

Moreover, cardiac hypertrophy is caused by several different mechanisms. As disclosed in Berman et al, cardiac hypertrophy can be caused by promotion of secretion of renin-aldosterone. Other causes include, for example, the endothelium system, immune system and thympathetic nervous system. *See,* M.A. Hefti et al, *J. Mol. Cell Cardiol.* 29:2873 (1997) (copy enclosed). Therefore, though Berman describes the use of ANP to inhibit secretion of renin-aldosterone, the reference fails to disclose or even suggest that ANP inhibits cardiac

hypertrophy caused by other mechanisms, or that cardiac hypertrophy can be inhibited without affecting blood pressure and urine volume, as instantly claimed.

Withdrawal of this rejection is thus respectfully requested and believed to be in order.

Claims 6 and 11-14 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Blaine or Berman or Neustadt. The Examiner alleges that it would have been obvious to one skilled in the art to modify the cited art to arrive at Applicant's claimed invention. This rejection is respectfully traversed.

As described above, none of the references disclose Applicants' claimed method of treatment. Nor would such a method as claimed be obvious based upon the cited art. There is no reason for one skilled in the art to expect, based upon Blaine, Berman or Neustadt, that a substance that acts on guanylyl cyclase A natriuretic peptide receptor and accelerates production of cyclic guanosine monophosphate is able to treat cardiac hypertrophy which is not based on diuretic and hypotensive effects.

In view of the above, withdrawal of the rejection is respectfully requested and believed to be in order.

In the event that there are any questions relating to this amendment, it would be appreciated if the Examiner would contact the undersigned attorney at 508-339-3684.

Further and favorable action in the form of a Notice of Allowance is respectfully requested and believed to be in order.

Respectfully submitted,

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